containing human constant domains and murine variable region [or] and a humanized antibody.

REMARKS:

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, Claim 34 has been revised in order to overcome the outstanding §112 objection thereto.

Turning now to the Office Action, the Examiner's withdrawal of many of the previous art rejections is acknowledged with appreciation. However, Claims 29-32, 34 and 37 stand rejected under 35 U.S.C. §102(e) as assertedly being anticipated by de Boer et al (USP 5,747,034), and further Claims 29 through 37 stand rejected under 35 U.S.C. §103 as assertedly being obvious over de Boer et al in view of art-known procedures and motivation to generate recombinant antibodies specific to a desired antigen. These rejections are respectfully traversed.

At the outset, it should be noted that the subject claims are directed to a monoclonal antibody which specific binds to human B7.1 antigen (CD80) and inhibits

the binding of B7.1 antigen to CD28, but which antibody does not inhibit the binding of B7.1 antigen to CTLA-4.

With respect to an antibody having such binding specificity, Applicants have carefully reviewed the de Boer et al reference and respectfully submit that there is no reasonable basis for concluding that the B7-24 antibody inherently meets the characteristics of the recited antibody. In this regard, the Examiner cites particular portions of the patent in support of his position that the B7-24 antibody inherently comprises the same binding specificity of the subject antibody. In particular, the Examiner references Col. 4, lines 49-65, Col. 6, lines 24-41, Col. 25, lines 28-30, and Cols. 27-28, Example 14, of the de Boer et al patent. However, Applicants respectfully submit that none of these sections support this proposition.

Specifically, the disclosure at Col. 5, lines 49-65, teaches that B7-24 antibody binds specifically to the B7.1 molecule and does not specifically to B7.2. Moreover, the Patentees further state that this is in contrast to the recombinant fusion protein of the CTLA-4 molecule, which binds to B7.1 and B7.2. Also, the patent states that the binding specificity of B7-24 is different from a prior antibody, specifically BB-1, which binds to B7.1 and to a third form of the B7 molecule, i.e., B7-3. However, there is no disclosure which would indicate that the B7-24 antibody, as with the present antibody, does not inhibit the B7.1-CTLA-4 interaction as was the case with prior antibodies having

specificity to B7.1. Moreover, the mere fact that this antibody binds to a distinct epitope than BB-1, also does not support the proposition that the B7-24 antibody does not inhibit the B7.1/CTLA-4 interaction. With respect to such position, Applicants respectfully note that different antibodies having specificity to B7.1 were known prior to the present invention having different epitopic specificities but, to Applicants' knowledge, all of such monoclonal antibodies inhibited both the B7.1/CD28 interaction and B7.1/CTLA-4 interaction. This is in contrast to the subject antibodies which selectively only inhibit the B7.1/CD28 interaction, and not the B7.1/CTLA-4 interaction.

Moreover, the disclosure at Col. 6, lines 24-41, further does not reasonably suggest that the B7-24 antibody of the de Boer et al does not inhibit the B7.1/CTLA-4 interaction. Rather, all this disclosure indicates is that the B7-24 antibody selectively binds to B7.1 but not to B7.2 or B7.3. However, it does not reasonably suggest that their antibody binds to an epitope which is selective to the interaction of B7.1 with CD28 and does not affect the interaction with CTLA-4.

Furthermore, the discussion at Col. 25, lines 28-30, of the patent further does not provide a reasonable expectation that the B7-24 antibody does not inhibit the B7/CTLA-4 interaction. All this discussion in the patent indicates is that there is apparent synergy between B7-24 and cyclosporin A. However, the Patentees do not speak to whether this antibody has any effect on the B7.1/CTLA-4 interaction.

Similarly, the discussion in Example 14 also does not provide a reasonable expectation that the B7-24 antibody comprises the same binding specificity as the antibodies of the present invention. As with the previous discussions, the Patentees merely teach that their monoclonal antibody binds to a distinct epitope on B7.1 than the BB1 monoclonal antibody, and a CTLA-4 Ig fusion protein. However, the patent does not contain any data which would suggest that the B7-24 antibody does not inhibit the B7.1/CTLA-4 interaction. More specifically, the patent teaches that, whereas CTLA-4 Ig binds to both B7.1 and B7.2, the B7-24 antibody apparently binds to a different epitope on B7.1 because it binds only to B7.1 and not to B7.2. However, this does not provide a reasonable expectation that B7-24 antibody would not also inhibit the B7.1/CTLA-4 interaction (as was the situation with previous anti-B7.1 antibodies).

Therefore, Applicants respectfully submit that the inherency-based §102 rejection should be withdrawn. Applicants respectfully maintain that the cited patent does not provide a reasonable expectation that the monoclonal antibody of the reference possesses the same binding specificity as the subject antibodies, namely selective inhibition of the CD28/B7 without inhibition of the CD28/CTLA-4 interaction.

With respect to such a rejection, it is acknowledged that when the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the

prior art, that they possess the authority to require an applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. However, before an applicant can be put to this burdensome task, the Patent Office must provide some evidence or scientific reasoning to establish the reasonableness of the Patent Office's position that the functional limitation is an inherent characteristic of the prior art. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. (With emphasis.) Ex Parte Skinner, 2 USPQ2d 1788, 1789 (PTO Bd App & Int 1987).

If inherency *could* be established by probabilities, then the probabilities in this case weigh in Applicants' favor. It has been known in the art for some time that B7 binds to both CD28 and CTLA-4, and that this is due to the sequence and structural homology between the two molecules. Indeed, murine CTLA-4 and CD28 cDNAs demonstrate approximately 76% homology (Harper et al. (1991) *J. Immunol.,*147: 1037; Howard et al. (1991) *Immunogenet.,* 33:74). Because of this homology, CTLA-4 was postulated to play a role in T-cell activation, which is precisely opposite of what its actual role has now been determined to be.

As reported in the draft manuscript attached to Applicants' previous Response dated October 14, 1997, CTLA-4 is now known to play a role in down-regulating immune responses after antigen exposure. In view of this disclosure, it has now become an

important goal to isolate antibodies that block CD28/B7 interactions but leave negative regulatory CTLA-4/B7 interactions intact, i.e. for the purpose of more effectively inhibiting T-cell activation in graft rejection and autoimmune disease. Before this realization, it was the goal of the skilled artisan to isolate antibodies that inhibited both CD28 and CTLA-4 interactions with B7. Thus, the antibodies of the prior art would be more likely to inhibit both types of interactions, if probabilities were the standard for determining inherency (which they are not), and if the goals of the skilled artisan were evaluated correctly by the level of knowledge in the art at the time.

Also, Applicants respectfully submit that the present invention is not rendered obvious by the de Boer et al patent. Essentially, the de Boer et al reference would not provide any motivation or provide a reasonable expectation that a monoclonal antibody having the recited binding specificity could be obtained. Rather, all the reference suggests is that antibodies having different epitopic binding specificities which bind to human B7.1 could be obtained. However, there is no specific teaching or suggestion with respect to the subject antibodies, which selectively inhibit the B7.1/CD28 interaction and do not inhibit interaction of B7.1 with CTLA-4. This is highly significant as the subject antibodies, based on such binding specificity, leave negative regulatory CTLA-4/B7 interactions intact, i.e., for the purpose of more effectively inhibiting T-cell activation and graft rejection and autoimmune disease. Moreover, Applicants respectfully submit that

the claimed functional limitation of failing to inhibit CTLA-4/B7 interaction is not an unexpected property of a B7 specific antibody. To the contrary, because B7 binds to both CTLA-4 and CD28, and given the fact that CTLA-4 and CD28 have a high degree of homology, antibodies that bind B7 and inhibit its interaction with CD28 would also be expected to inhibit interaction with CTLA-4, absent evidence to the contrary.

As described in the draft manuscript attached to Applicants' Response submitted on October 14, 1997, the subject antibodies were obtained following immunization of cynamologous primates and the isolated antibodies were engineered into primatized versions (by substituting human constant regions). Based on the known homology of CD28 and CTLA-4, it was both fortunate and unexpected, especially in view of the now understood role of CTLA-4, that the inventors were able to isolate antibodies that bind to human B7.1 but fail to inhibit CTLA-4 interaction.

Therefore, based on the foregoing, withdrawal of the §103 rejection based on the de Boer et al reference is respectfully requested.

In view of the foregoing remarks, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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Date: February 17, 1999